N-terminal Pro-brain Natriuretic Peptide plasma levels are Associated With a Short-Term Diagnosis of Cancer in Patients with Coronary Artery Disease

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Abstract

Background NT-proBNP plasma levels may predict a future cancer diagnosis(CD)in patients with coronary artery disease(CAD).In this paper we test whether this could merely represent the detection of increased NT-proBNP levels in subclinical tumors. Methods We studied 962 patients with stable CAD and free of cancer and heart failure at baseline. NT-proBNP, galectin-3, monocyte chemoattractant protein-1,high-sensitivity C-reactive protein, high-sensitivity cardiac troponin I(hsTnI),and calcidiol plasma levels were assessed.The primary outcome was new CD. Results After 5.40(2.81-6.94)years of follow-up,59 patients received a CD.We divided the population in three subgroups: those not developing cancer during follow-up (group A;N=903),and those receiving a CD in the first 3 years of follow up(group B; N=30),or later (group C;N=29).At baseline, 3.3% of patients of group B,0.0% in groups C and 12.3% in group A(p=0.036) presented a previous history of heart failure.In group B,NT-proBNP[HR1.036 CI(1.015-1.056)per increase in 100 pg/ml;p=0.001],previous atrial fibrillation[HR3.140 CI(1.196-8.243);p=0.020],and previous heart failure[HR0.067 CI(0.006-0.802);p=0.033]were independent predictors of CD at multivariate analysis.In group C there were not significant predictors of CD. Conclusions In patients with CAD,NT-proBNP is an independent predictor of CD in the first three years of follow-up,but not later,suggesting that it could be detecting subclinical undiagnosed cancers.New studies in large populations are needed to confirm these findings. What is already known about this topic? It has been linked in previous studies that NT-Pro-BNP elevation could be related to future diagnosis of some cancers especially renal tumors. It has also seen that NT-ProBNP is related to mortality in cancer patients.Finally, our group has previously seen that NT-Pro-BNP predicts cancer diagnosis in patients with myocardial infarction. What does this article add? According to our previous investigations this study support the idea that NT-Pro-BNP is a good marker for further cancer diagnosis not only in patients with myocardial infarction but across the spectrum of the whole CAD

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NT-proBNP predicts short-term cancer diagnosis

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The authors declare no conflict of interest

ABSTRACT

Background

N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma levels may predict a future cancer diagnosis (CD) in patients with coronary artery disease (CAD). In this paper we test whether this could merely represent the detection of increased NT-proBNP levels in subclinical tumors.

Methods

We studied 962 patients with stable CAD and free of cancer and heart failure at baseline. NT-proBNP, galectin-3, monocyte chemoattractant protein-1, high-sensitivity C-reactive protein, high-sensitivity cardiac troponin I (hsTnI), and calcidiol plasma levels were assessed. The primary outcome was new CD.

Results

After 5.40 (2.81-6.94) years of follow-up, 59 patients received a CD. We divided the population in three subgroups: those not developing cancer during follow-up (group A; N=903), and those receiving a CD in the first 3 years of follow up (group B; N=30), or later (group C; N=29). At baseline, 3.3% of patients of group B, 0.0% in groups C and 12.3% in group A (p=0.036) presented a previous history of heart failure. In group B, NT-proBNP [HR 1.036 CI (1.015-1.056) per increase in 100 pg/ml; p=0.001], previous atrial fibrillation [HR 3.140 CI (1.196-8.243); p=0.020], and previous heart failure [HR 0.067 CI (0.006-0.802); p=0.033] were independent predictors of CD at multivariate analysis. In group C there were not significant predictors of a CD.

Conclusions In patients with CAD, NT-proBNP is an independent predictor of CD in the first three years of follow-up, but not later, suggesting that it could be detecting subclinical undiagnosed cancers. New studies in large populations are needed to confirm these findings.

Keywords: Coronary artery disease, N-terminal pro-brain natriuretic peptide, cancer.

What is already known about this topic?

It has been linked in previous studies that Nt Pro-BNP elevation could be related to future diagnosis of some cancers especially renal tumors. It has also seen that Nt-ProBNP is related to mortality in cancer patients. Finally, our group has previously seen that Nt Pro-BNP predicts cancer diagnosis in patients with myocardial infarction.

What does this article add?

According to our previous investigations this study support the idea that Nt Pro-BNP is a good marker for further cancer diagnosis not only in patients with myocardial infarction but across the spectrum of the whole coronary artery disease (stable and unstable)

BACKGROUND

Patients with coronary artery disease (CAD) are at risk of developing malignancies, given that cancer shares some risk factors with this disorder, as age, smoking, and even some dietary patterns[1-3]. Then, finding biomarkers that predict both the risk of cancer and of cardiovascular events could be useful in CAD patients.

Natriuretic peptides are secreted by cancer cells[4, 5]and N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) levels are increased in patients with cancer[6]. Previously, we have reported that NT-proBNP plasma levels predict a future diagnosis of cancer in 704 patients with CAD from the Biomarkers in Acute Coronary Syndrome & Biomarkers in Acute Myocardial Infarction (BACS & BAMI) studies[7]. We launched the hypothesis that NT-proBNP could be merely detecting subclinical cancers rather than being a real predictor. Now we try to support this hypothesis by analyzing if this biomarker predicts a new cancer diagnosis only in the short-term but not in the long-run. For that purpose we have expanded the sample size and the follow-up of the same population, studying 962 patients with CAD free of malignancies at baseline, who developed 59 cancers at follow-up. We divided them into those receiving a cancer diagnosis in the first three years and those receiving this diagnosis beyond this time. Along with NT-proBNP, we also tested these biomarkers: monocyte chemoattractant protein-1 (MCP-1), involved in inflammation and atherothrombosis, among other processes[8, 9]; galectin-3, related to malignancies, heart failure, thrombosis, and renal dysfunction[10, 11]; high-sensitivity cardiac troponin I (hsTnI), which has been described to have prognostic value in stable CAD[12]; and vitamin D (calcidiol) plasma levels, as low levels of this molecule have been related to cancer[13]. High-sensitivity C-reactive protein (hsCRP) was studied as a reference given the large amount of information published on this biomarker on cardiovascular disease.

METHODS

Patients

The BACS & BAMI studies included patients admitted to hospitals Fundación Jiménez Díaz, Fuenlabrada, Móstoles, Alcorcón, and Puerta de Hierro with either non-ST elevation acute coronary syndrome or ST-elevation myocardial infarction. Inclusion and exclusion criteria have been detailed previously[14].

The research protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinky as reflected in a priori approval by the human research committees of the institutions participating in this study. All patients signed informed consent documents.

Study Design

In addition to plasma withdrawal at discharge, in the BACS & BAMI studies a second plasma sample was extracted 6-12 months later, on an outpatient basis, with the patients in a stable clinical situation. This paper is a sub-study of the BACS & BAMI studies, and reports the clinical and analytical findings obtained at this second plasma extraction, relating them to subsequent follow-up. Then, the moment of this second plasma extraction is considered to be the baseline visit of this sub-study. At this point, all patients were free of a diagnosis of cancer and even of any symptoms or signs suggesting this diagnosis.

Figure 1 shows the flow chart for patient selection. The baseline visit for this sub-study took place between January 2007 and December 2014. At this moment, clinical variables were recorded and 12-hour fasting venous blood samples were withdrawn. The last follow-up visits took place in June 2016 and included both, a review of the clinical records and an on-site visit or telephone contact.

The primary outcome was the development of a new cancer with histological confirmation, excluding non-melanocytic skin tumors.

Analytical Studies

Blood samples were collected in Ethylene-Diamine-Tetra-Acetic Acid and centrifuged at 2,500 g for 10 minutes and plasma was stored at -80°C. Patients were seen every year at their hospital.

The investigators who performed the laboratory determinations were unaware of the clinical data. Plasma concentrations of MCP-1 and galectin-3 were determined in duplicate using commercially available enzyme-linked immunosorbent assay kits (DCP00, R&D Systems and BMS279/2 Bender MedSystems respectively) following the manufacters' instructions. Hs-CRP was assessed by latex-enhanced immunoturbidimetry (ADVIA 2400 Chemistry System, Siemens, Germany), NT-pro-BNP by immunoassay (VITROS, Orthoclinical Diagnostics, U.S.A.), and hsTnI was assessed by direct quimioluminiscence (ADVIA Centaur, Siemens, Germany). Plasma calcidiol levels were quantified by chemiluminescent immunoassay (CLIA) on the LIAISON XL analyzer (LIAISON 25OH-Vitamin D total Assay DiaSorin, Saluggia, Italy). Lipids, glucose, and creatinin were determined by standard methods (ADVIA 2400 Chemistry System, Siemens, Germany).

Statistical Analysis

Quantitative data following a normal distribution are displayed as mean±Standard deviation and compared using the Student t-test and the ANOVA (Analysis of Variance) for two and three comparisons, respectively. Quantitative data not following a normal distribution are displayed as median (interquartile range) and compared using the Mann-Witney and the Kruskal-Wallis tests for two and three comparisons, respectively. Qualitative variables are displayed as percentages and compared by χ^2 or Fisher exact test when appropriate. Univariate Cox regression analysis was used to study the predictive power of the variables studied. Multivariate Cox regression analysis was performed including all variables showing $p<0.20$ at univariate analysis.

Analyses were performed with R v3.5.1 (R foundation for Statistical Computing, Viena, Austria) and SPSS 19.0 (SPSS Inc., New York).. Statistical significance was set at $p<0.05$ (two-tailed).

RESULTS

Population of the study

We included 964 patients with stable CAD. Two patients were lost to follow-up, leaving 962 patients for the analysis, who were followed for an average period of 5.40 (2.81-6.94) years.

Of the 962 patients studied, 59 developed cancer during follow-up. We divided the sample in three subgroups: patients who did not develop cancer during follow-up (group A; N=903), those receiving a cancer diagnosis in the first 3 years of follow-up (group B; N=30), and patients receiving a cancer diagnosis beyond 3 years (group C; N=29). Table 1 shows the baseline characteristics of the patients.

In the group B there were 15 (50.0%) carcinomas, 11 (36.7%) adenocarcinomas, 3 (10.0%) cancers with other histology, and 1 (3.3%) case of unknown etiology. In group C these values were 13 (44.8%), 11 (37.9%), 5 (17.2%), and 0 (0.0%), respectively. The case of unknown histology corresponded to a 83-year-old man with images clearly compatible with lung cancer with metastases, who was dying and the doctors decided not to perform histological analysis. Table 2 shows the locations of the cancers.

NT-proBNP plasma levels predict a future diagnosis of cancer

We performed a univariate Cox analysis for all the variables displayed in table 1. Age [HR 1.034 CI (1.003-1.065); p=0.032], NT-proBNP (HR 1.020 [1.004-1.035] per 100 units of increment; p=0.012), hsTnI plasma levels (HR 1.052 [1.005-1.102] per 0.1 unit; p=0.029), and the previous existence of atrial fibrillation [HR 3.144 CI (1.203-8.216); p=0.019] were independent predictors of a future diagnosis of cancer in the first three years (Supplemental Table S1). No variable was shown to predict a cancer diagnosis beyond three years of follow-up.

Variables that showed a p value <0.20 at the univariate analysis were included in the multivariate Cox regression. NT-proBNP was a strong, independent predictor of developing cancer in the first three years of follow-up, along with the existence of previous atrial fibrillation and the absence of heart failure (Table 3). There were no independent predictors of developing cancers beyond three years of follow-up.

Forty patients (4.4%) developed heart failure during follow-up in the group A, 0 (0.0%) in group B, and 2 (6.9%) in group C (p=0.216).

NT-proBNP plasma levels in different types of cancers diagnosed before three years of follow-up

In the subgroup of patients developing cancer in the first 3 years of follow-up, NT-proBNP levels were 519.8±706.5 (N=15) in those with carcinoma and 480.4±143.0 pg/ml (N=11) in patients developing adenocarcinoma (p=0.877). Lung and hematologic cancers (n=6) did not have NT-proBNP levels significantly different to other tumors (n=24) (428.5 [152.3, 1212.0] vs 257.5 [88.0, 981.3] pg/ml; p=0.402).

DISCUSSION

Patients with CAD have high probabilities of developing tumors, given that the incidence of cancer increases with age[1], tobacco consumption and some dietary patterns that also promote CAD[2, 3]. Thus, predicting the risk of cancer in this population would be interesting.

NT-proBNP is mainly used in diagnosing heart failure[15], although it may also predict the development of heart failure and death in patients with cardiovascular disease[14, 16]. In addition, it has been associated with total death in elderly subjects[17-20].

In 2015 we described for the first time that NT-proBNP is an independent predictor of the appearance of malignancies in patients with CAD[7]. However, we hypothesized that probably NT-proBNP levels could be really a marker of subclinical tumors rather than a real predictor of the development of new cancers. To test this hypothesis we have expanded the sample size and extended the follow-up period of the same series of patients, reporting a total of 59 patients developing cancer instead of the 24 cases reported previously. Then, we divided the patients receiving a new cancer diagnosis during the follow-up into those receiving this diagnosis before and after three years. NT-proBNP was an independent predictor of developing a cancer in the first three years of follow-up, but not later.

The likelihood that concomitant heart failure may have influenced our results is very slim. First, the presence of previous heart failure was very low in the whole sample and significantly lower in patients developing a cancer in the first three years as compared with patients with no cancer at follow-up. Second, a low percentage of our patients developed heart failure during follow-up, without significant differences between the cancer and non-cancer groups. Interestingly, no patient in the group receiving a cancer diagnosis in the first three years developed heart failure during follow-up. Also, variables that may influence NT-proBNP levels, such as age, sex, hypertension, atrial fibrillation, glomerular filtration rate and body-mass index[16, 21, 22] were included in the analysis, limiting the possibility that they could have influenced the results.

Natriuretic peptides are used in patients with cancer mainly as predictors of cardiac toxicity secondary to chemotherapy[23]. However, a potential relationship between plasma levels of these peptides and cancer itself has been suggested, and patients with cancer may have elevated BNP levels in the absence of heart failure[6, 24]. In patients >40 years of age with previous non-cardiac surgery, NT-proBNP levels[?]125 pg/ml were independently associated with lung cancer after excluding cases with heart failure, CAD, and other conditions known to affect this biomarker[25]. Although natriuretic peptides have been shown to be secreted by small-cell lung cancer[5], only 15% of the cases reported in this previous study, and around 17% in the present paper, had this type of cancer, suggesting that other tumors could also produce NT-proBNP. In addition, NT-proBNP was an independent predictor of survival in patients with non-Hodgkin lymphoma[26]. Of interest, NT-proBNP levels were associated with the involvement of two or more extranodal sites, suggesting a potential relationship with the stage of this malignancy. Similarly, increased NT-proBNP plasma levels predict the progression and worse outcome of metastatic renal carcinoma[27, 28]. In this regard, elevated NT-proBNP levels were reported to be associated with total mortality in patients with cancer and no previous cardiotoxic anticancer therapy who were stable from a cardiovascular point of view[29].

Cancer cells may produce natriuretic peptides. Small-cell lung cancer may secrete both pro-atrial natriuretic peptide and BNP[4, 5]. Also, BNP is expressed in normal adrenal glands and in adrenal tumors[30]. NT-proBNP synthesis may be stimulated by several proinflammatory cytokines[31] that, for instance, are expressed in Hodgkin lymphoma[32, 33]. Moreover, these cytokines may predict clinical outcome in diffuse large B-cell lymphomas[34-36] and are increased in malignancies at advanced stages[26].

The specific cause of the elevation of natriuretic peptide plasma levels seen in cancer has not yet been elucidated. It has been demonstrated that these peptides decrease the number of several cancer-cell types in vitro through a reduction of DNA synthesis[37] and inhibition of c-Fos and c-Jun protooncogenes[38]. They also diminish the expression of vascular endothelial growth factor and that of its receptor VEGFR2, thus suggesting that these peptides have the potential to control vasculogenesis[39]. One work has shown opposite effects of natriuretic peptides on carcinogenesis depending on their concentrations[40]. Overall, natriuretic peptides seem to decrease the proliferation of cancer cells. Accordingly, they inhibit lung metastases and skin carcinogenesis in animal models[41, 42].

Given that most data suggest an anti-cancer effect of natriuretic peptides, it is plausible that their production by cancer cells represents a negative feed-back mechanism trying to control tumor growth. Of interest, in our study, NT-proBNP was only useful in predicting tumors that were diagnosed in the first three years of follow-up, losing its predictive power beyond this time. This supports the hypothesis that NT-proBNP actually detects tumors that are present subclinically at the moment of blood extraction and which are not evident using the tools currently available in clinical practice. In that case, NT-proBNP could be useful for early detection of malignancies, as not all the cancers described in this paper have a specific biomarker to aid in diagnosis.

This work has certain limitations. 1) The inverse association between previous heart failure and future cancer must be interpreted with caution, due to the low percentage of patients with heart failure in addition to the limited number of them who developed cancer during follow-up. 2) Given the relatively low number of patients who developed cancer, these findings should be confirmed in other populations. 3) Also, given the limited number of patients who developed cancer we could not establish whether the predictive effect of NT-proBNP is restricted to some types of cancer or can be applied to any malignancy.

Conclusions

NT-proBNP is an independent predictor of malignancies in the short-term in patients with stable CAD. If these findings are confirmed in further studies, this biomarker could be helpful in assessing the global prognosis in patients with CAD.

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TABLE 1. Baseline characteristics of patients

Characteristic	Patients without cancer (N=903)	Patients with cancer in 3 years (N=30)	Patients with cancer beyond 3 years (N=29)	P Value
Age (yr)	61.1 ± 12.0	66.0 ± 11.6	62.2 ± 12.3	0.083
Male sex (%)	23.5	30.0	27.6	0.632
Body-mass index (Kg/m^2)	28.5 ± 4.35	27.8 ± 4.71	28.8 ± 3.78	0.621
Diabetes (%)	24.0	16.7	31.0	0.434
Present Smoker (%)	14.0	13.3	10.3	0.955
Present or past smoker (%)	75.6	86.7	75.9	0.380
Hypertension (%)	63.5	80.0	72.4	0.115
Previous heart failure (%)	12.3	3.3	0.0	0.036
Peripheral artery disease (%)	3.8	3.3	3.4	1.000
Cerebrovascular events (%)	2.9	0.0	3.4	0.660
Ejection fraction < 40% (%)	6.9	6.9	10.7	0.585
Present or past atrial fibrillation (%)	6.0	16.7	6.9	0.064

Characteristic	Patients without cancer (N=903)	Patients with cancer in 3 years (N=30)	Patients with cancer beyond 3 years (N=29)	P Value
MEDICAL THERAPY				
Acetylsalicylic acid (%)	92.6	96.7	89.7	0.556
AntiP2Y12 (%)	75.7	76.7	51.7	0.013
Acenocumarol (%)	5.2	3.3	3.4	1.000
Statins (%)	94.5	93.3	93.1	0.567
Oral antidiabetic drugs (%)	16.9	10.0	24.1	0.351
Insulin (%)	7.0	0.0	0.0	0.150
ACEI (%)	62.5	63.3	44.8	0.155
Angiotensin receptor blockers (%)	15.0	13.3	24.1	0.370
Aldosterone receptor blockers (%)	7.0	6.7	3.4	0.919
Betablockers (%)	78.8	73.3	65.5	0.184
Diuretics (%)	18.8	23.3	27.6	0.422
Amiodarone	0.9	0.0	0.0	1.000
Digoxine	0.3	0.0	0.0	1.000
ANALYTICAL DATA				
LDL cholesterol (mg/dl)	80.5 ± 25.0	78.1 ± 25.2	85.3 ± 22.5	0.518
HDL cholesterol (mg/dl)	42.0 ± 10.8	43.4 ± 10.7	44.5 ± 13.6	0.397
Non-HDL cholesterol	104 ± 30.5	98.4 ± 27.1	111 ± 28.2	0.291
Triglycerides (mg/dl)	101 (66.0)	92.5 (66.2)	121 (56.0)	0.135
Glycemia (mg/dl)	101 (24.0)	98.0 (17.8)	99.0 (19.0)	0.792
eGFR (CKD-EPI) (ml/min/1.73 m^2)	78.6 ± 19.4	74.4 ± 19.2	73.1 ± 17.8	0.171
Hs C-reactive protein (mg/l)	1.08 (2.72)	2.68 (4.63)	1.49 (2.81)	0.004
NT-ProBNP (pg/ml)	176 (297)	272 (815)	155 (217)	0.324
MCP-1 (pg/ml)	135 (74)	151 (58)	133 (43)	0.725
Galectin-3 (ng/ml)	7.86 (3.89)	7.85 (4.13)	7.50 (2.89)	0.253

Characteristic	Patients without cancer (N=903)	Patients with cancer in 3 years (N=30)	Patients with cancer beyond 3 years (N=29)	P Value
Hs troponin I (ng/ml)	0.003 (0.010)	0.002 (0.016)	0.003 (0.009)	0.837
Calcidiol (ng/ml)	20.4 ± 8.55	21.4 ± 9.8	17.6 ± 6.93	0.175

Values are presented as mean±Standard deviation and median (Interquartile range)

ACEI: Angiotensin-converting inhibitors; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: Estimated glomerular filtration rate; HDL: high-density lipoprotein; Hs: High-sensitivity; LDL: low-density lipoprotein MCP-1: monocyte chemoattractant protein-1; NT-Pro-BNP: N-terminal pro-Brain natriuretic peptide.

TABLE 2. Location of the cancers developed at follow-up

Cancer location	Cancer <3 years	Cancer >3 years
Prostate	5 (16.7%)	6 (20.7%)
Liposarcoma	1 (3.3%)	0 (0%)
Esophagus	1 (3.3%)	1 (3.4%)
Pancreas	2 (6.7%)	1 (3.4%)
Melanoma	1 (3.3%)	1 (3.4%)
Pharynx and mouth	1 (3.3%)	2 (6.9%)
Uterus	0 (0%)	1 (3.4%)
Liver and biliary system	0 (0%)	1 (3.4%)
Colon	3 (10%)	3 (10.3%)
Lung	5 (16.7%)	5 (17.2%)
Leukemia	0 (0%)	1 (3.4%)
Larynx	3 (10%)	0 (0%)
Urinary bladder and Ureter	2 (6.7%)	1 (3.4%)
Breast	2 (6.7%)	2 (6.9%)
Lymphoma	1 (3.3%)	1 (3.4%)
Kidney	3 (10%)	3 (10.3%)

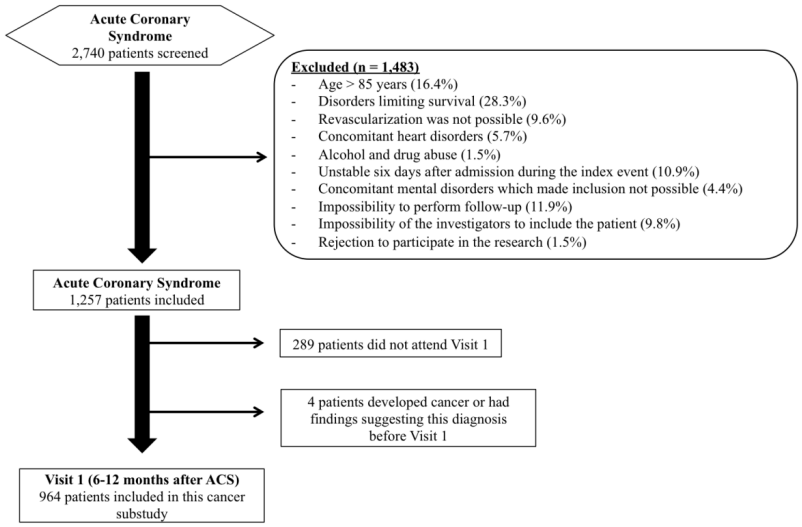
TABLE 3.- Multivariate analysis showing the predictors of a cancer diagnosis before 3 years of follow-up.

	Hazard Ratio (95% CI)	p
NT-proBNP	**1.036 (1.015, 1.056)**	**0.001**
Atrial fibrillation	**3.140 (1.196, 8.243)**	**0.020**
Heart failure	**0.067 (0.006, 0.802)**	**0.033**

CI: Confidence Interval; NT-proBNP: N-terminal pro-brain natriuretic peptide

FIGURE LEGENDS

Figure 1. Flow-chart of patient inclusion. ACS: Acute Coronary Syndrome.



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